Evaluations of New Indications

Corticosteroid Aerosols in the Treatment of Asthma

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Since the 1950s, corticosteroid aerosols have proved useful in the treatment of asthma. Although their precise mechanism of action is not known, these topical agents have beneficial antiinflammatory and decongestive effects on the bronchial tree in both the allergic and nonallergic forms of this disease. Four of the newer aerosolized steroids — beclomethasone dipropionate, triamcinolone acetonide, flunisolide and budesonide — have been evaluated in clinical trials. The last drug is still investigational. Their side effects are minimal, the major ones being oral candidiasis and dysphonia. They are most effective when used prophylactically and should not be administered during acute asthmatic attacks, as insufficient amounts of drug are inhaled when the airways are constricted. Patients must be instructed in the correct techniques of administering steroid aerosols to ensure optimal therapy.
(Pharmacotherapy 1984;4:334–342)

OUTLINE

Aerosolized preparations of corticosteroids were proposed for the treatment of asthma in the early 1950s, beginning with studies of topical cortisone by Gelfand.[1] These studies were performed on the theory that high local concentrations of steroids would be as effective on diseased bronchial mucous membranes as when steroids were applied to the skin or injected into joints. It was also postulated that these locally acting agents might relieve asthma symptoms with fewer side effects than systemically administered steroids. After Gelfand reported successful results in 5 patients, other investigators explored the efficacy of hydrocortisone inhaled either as a powder or as a solution.[2-4] They concluded that aerosolized hydrocortisone benefitted relatively few patients and gave no evidence that systemic side effects would be diminished.

Dexamethasone phosphate, a water-soluble ester, was the first of the next generation of topical corticosteroids to be studied as an aerosol preparation.[5] This potent antiinflammatory drug was first investigated in 1962 in the hope that it would gain access to the bronchial tree as far as the terminal respiratory bronchioles and mix with bronchial secretions for better effects. Dexamethasone phosphate was found to be consistently effective in reducing oral steroid requirements and suppressing asthma symptoms in both adults and children.[6-8] However, investigators also found that it produced unwanted systemic side effects such as moon facies and decreased urinary cortisol metabolites.[9-12] In addition, Dennis and Itkin reported that 5 patients developed oral thrush after using dexamethasone aerosol.[13] Although effective in suppressing asthma, this preparation did not seem to have selective topical action on the bronchial mucous membrane, but rather was systemically absorbed in the tracheobronchial tree.[14]

These early clinical experiences revealed that there were no obvious advantages in using hydrocortisone or dexamethasone by the inhalation route.

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Therefore it was essential that new inhalation steroid compounds be developed that would provide optimal topical effects but have poor absorption properties.

Structural Activity Relationships

The ideal glucocorticoid for local treatment of asthma would act in the lung but produce a minimum of systemic effects in the therapeutic dose range. To achieve this, the compound should combine properties of selective topical activity with poor absorption or rapid inactivation after absorption (i.e., low bioavailability and short plasma half-life).

For some time it was known that compounds could be synthesized with properties of enhanced glucocorticoid activity and reduced mineralocorticoid effects by modifying the hydrocortisone molecule in positions 1, 2, 6, 9, 16 and 17 (Figure 1). These potent agents (e.g., prednisolone) have poor topical effects, however.[14] To achieve enhanced topical corticosteroid action, some of the hydroxyl groups in the hydrocortisone molecule were substituted with ester acetonide groups (Figure 1). Among these potent glucocorticoids with desired topical activity were beclomethasone 17α, 21-dipropionate and betamethasone 17-valerate (Figure 2). Pharmaceutical chemists also developed compounds, such as triamcinolone acetonide and flunisolide, with desired topical activity by substituting asymmetric 16α and 17α acetal groups.[15]

It was also demonstrated that the introduction of halogen substituents in the 6α, 9α or both positions would increase glucocorticosteroid activity;[16] however, there was no evidence that these halogen substitutions preferentially increased topical activity. Indeed, steroid nucleus fluorination in the 6α and 9α positions appeared to potentiate systemic activity more than the topical activity because it decreased systemic metabolism and transcortin binding.[17]

Brattsand and co-workers studied the influence of steroid nucleus fluorination on the topical and the systemic activity of 16α and 17α acetals and found that to obtain high topical and antiinflammatory activity, optimal fluorination of those groups was more important than it was of the 6α and 9α positions.[17] With this theory in mind, chemists developed budesonide, a compound with a high topical:systemic activity ratio (Table 1, Figure 2).

Modes of Action

The mechanism of action of steroids in asthma is not well understood. It is hypothesized that the free steroid molecule diffuses through the cell membrane where it forms an intracellular complex with a specific receptor protein.[18, 19] This complex is then transported into the cell nucleus where it is bound to specific parts of the chromatin and forms a new type of specific mRNA. This mRNA then determines the DNA and amino acid sequences for the synthesis of new proteins, which are responsible for steroid-specific cellular responses.

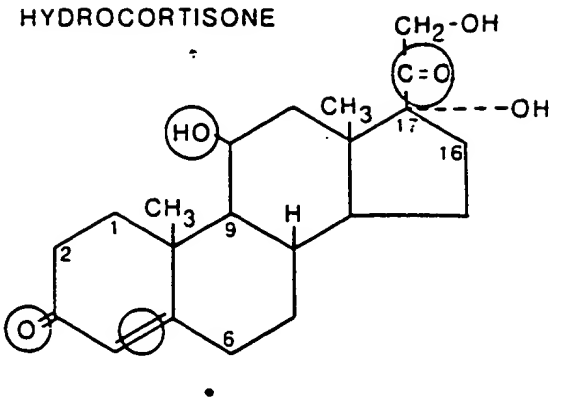

Figure 1. Structural formula of hydrocortisone. Groups that are essential to antiinflammatory activity are circled.

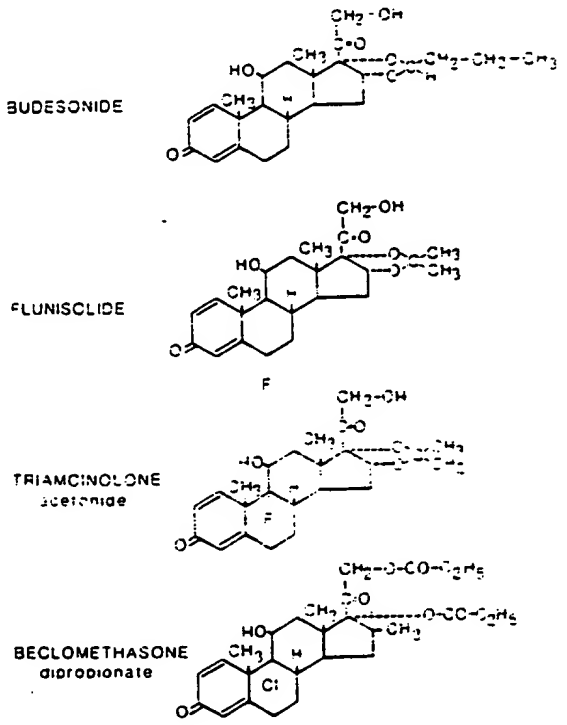

Figure 2. Structural formulas of 4 topically selective glucocorticosteroids. Budesonide is not yet available in the United States for the treatment of asthma. Flunisolide is also approved as a topical agent for the treatment of allergic rhinitis.

Table 1. Relative Potencies of Topically Selective Glucocorticosteroids in Inhibiting Rat or Mouse Ear Edema Formation and Thymus Involution after Topical Application

Compound	Topical Antiinflammatory Potency	Systemic Potency	Ratio of Topical to Systemic Potency
Budesonide	1	1	1
Beclomethasone dipropionate	0.4	3.5	0.11
Flunisolide	0.7	12.8	0.05
Triamcinolone acetonide	0.3	5.3	0.05

Adapted from reference 17.

The synthesis of proteins such as lipomodulin and macrocortin in response to steroidal stimulation is believed to inhibit the action of membrane phospholipase A_2 on the arachidonic acid cascade.[23,24] This results in inhibition of phospholipid methylation in the cell membrane and the formation of leukotrienes, prostaglandins, thromboxanes and other arachidonic acid metabolites.[24] Consequently, leukotriene-mediated effects such as chemotaxis, histamine release from mast cells and basophils, bronchospasm and inflammatory edema are suppressed.

In theory, the most beneficial effects of steroids in the treatment of asthma are their antiinflammatory and decongestive effects on bronchial mucous membranes. Thus corticosteroids are effective in allergic and nonallergic asthma because the inflammatory process occurs in both conditions.[23] Steroids may stabilize the vascular wall, with reduction of edema and inhibition of migration of inflammatory cells into bronchial tissues.

During allergen challenge, mast cells present in airway lumina release mediators and reduce permeability changes in the usually tight intercellular junctions of the respiratory mucosa, thus facilitating more allergen-mast cell contact and augmenting antigen mediator penetration into the submucosa. Aerosolized steroids are thought to depress these alterations of epithelial and endothelial cell permeability.[24]

Corticosteroids also possess a conditioning or so-called permissive effect on adrenergic receptors.[23] Through this effect they may enhance the effects of β-adrenergic agonists in asthma.

Other steroidal effects in controlling asthma include decreased leukocyte function and eosinopenia, which are beneficial in preventing tissue injury.[25,26]

Beclomethasone Dipropionate

Beclomethasone dipropionate aerosol (BDP) (Beclovent, Vanceril) first became commercially available in the United States as an inhaler in 1976. It has enhanced topical antiinflammatory activity compared to other topical steroids — dexamethasone phosphate, triamcinolone acetonide and betamethasone valerate — when tested by the vasoconstriction assay method described by McKenzie.[27] A dose of 400 μg of BDP per day is comparable to 5–10 mg of oral prednisone in the control of asthma.[28]

Also, BDP is shown to be effective in controlling asthmatic symptoms in steroid-dependent adults and children.[29–32] It has the advantage over oral corticosteroids in that it is relatively free of systemic side effects. It presents no risk to growth and development in pediatric patients.[33] Although systemic absorption is insignificant, slight adrenal suppression based on plasma cortisol determination, urinary free cortisol excretion and the 11-desoxycortisol response to metyrapone) due to inhaled BDP has been reported.[29–31] In the great majority of patients, this occurred at doses larger than 1600 μg per day.[29,32] Klein and colleagues reported no evidence of adrenal suppression in children using 400 μg of BDP per day.[33]

The usual daily dose of BDP in controlling asthma in adults is 400 μg, but some patients may require 800–1000 μg d. Higher doses may be required particularly in patients whose asthma was previously controlled with 10–15 mg of systemic prednisone daily.[34,35] Although most patients can eliminate the need for oral steroids by using 400 μg of BDP per day, those who usually take more than 10 mg of prednisone per day to control their asthma symptoms may benefit from a combination of a small oral dose of prednisone and a higher dose of BDP. Thus BDP achieves the same total corticosteroid effect but with less risk of systemic side effects.

Dosing Frequency

Although the manufacturers recommend using BDP 3–4 times daily in divided doses, less frequent schedules have been reported. Dosing 2 times a day was not significantly different from 4 times daily when both regimens provided the same total daily doses.[36] The advantages of the twice-daily regimen were improved patient compliance and possibly fewer local side effects. Since peak effects of steroids subside after 6–8 hours in general, however, it may

be preferable to use a more frequent dosing (i.e., 4 times daily) schedule until a steady state has been reached.[36]

Proper Inhalation Techniques

Successful corticosteroid aerosol therapy depends on efficient intrapulmonary drug delivery. Many patients do not use the metered-dose inhaler (MDI) skillfully, and as a result treatment may fail by default of the drug delivery system rather than the drug itself. It is therefore very important that patients be instructed about proper inhalation techniques.[37] With the MDI held a short distance from the open mouth, the patient should start inspiration from functional residual capacity. Inspiration should be slow and steady. Activation of the inhaler should be after inspiration has begun and the patient should continue inhaling to total lung capacity and hold the breath for a period of 10 seconds. The second actuation of aerosol medication should be done 2 or 3 minutes after the first dose. Patients are instructed about careful mouth washing with tap water after the delivery of inhaled medication.

The use of a spacer fitted into the MDI has been recommended in asthmatic children and in patients who use their conventional MDI ineffectively. Spacers have been shown to decrease oropharyngeal deposition of inhaled aerosols and to increase intrapulmonary deposition of aerosolized materials.[38] The frequency of oropharyngeal complications and the need for antifungal therapy are greatly reduced with the use of spacers. They would be particularly useful for selected patients whose response to inhaled steroid is compromised by dose-limiting oropharyngeal complications and to those who need a greater antiasthmatic effect.[38]

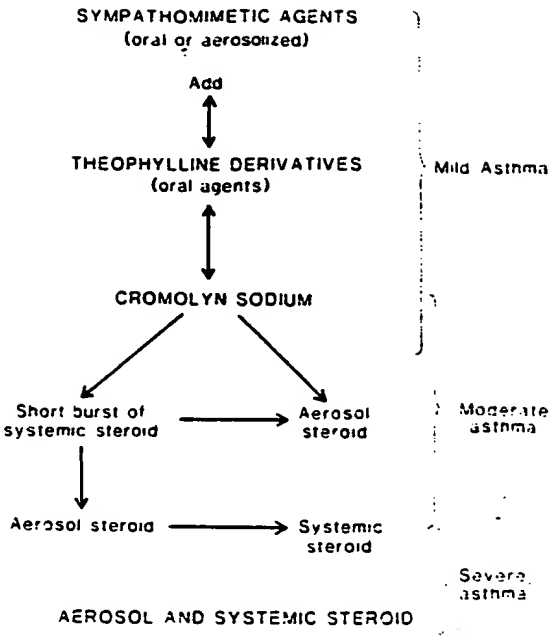

Figure 3. Steps in treating chronic asthma. Adapted from reference 28.

Use with Other Drugs

Although BDP can be used concurrently with other antiasthmatic drugs, it should be reserved for patients who fail to respond to conventional asthma therapy (Figure 3). Most patients with mild asthma can be treated successfully with bronchodilator drugs (beta agonists, theophylline) and cromolyn sodium. In severe disease or when asthma symptoms become chronic and labile, corticosteroids should be used. Like cromolyn sodium, BDP has no effect during an acute attack of asthma, and should not be used for this purpose.

In general, more than 50% of steroid-dependent patients with asthma can be maintained free of oral steroids most of the time while taking BDP.[26] Patients previously unable to convert to alternate-day prednisone can do so during BDP therapy.[39] Care must be taken, however, when switching from systemic to aerosol steroids. Oral prednisone must be tapered slowly because sudden discontinuation could cause uncomfortable systemic symptoms or even precipitate adrenal failure. During periods of stress, upper respiratory infections or exacerbations of severe asthma, it is crucial that generous amounts of oral steroids be added to the aerosol regimen until the acute crisis has subsided.

Side Effects

The most widely reported side effect of BDP is oropharyngeal candidiasis (oral thrush). It is dose-related and causes symptoms in about 5% of patients.[33,36] It is relatively trivial from the clinical point of view and usually responds to a single course of nystatin. Patients need to be reminded about rinsing their mouths with water or mouthwash after each inhalation dose. Dysphonia affects up to 50% of users and occasionally can be severe and persistent.[36] Toogood and associates reported the advantages of using two spacers in aerosolized corticosteroid delivery to reduce oropharyngeal candidiasis and double antiasthmatic potency.[38]

Other associated symptoms such as exacerbation of eczema or rhinitis may occur when a patient whose symptoms were previously suppressed by oral steroids is changing from systemic steroids to aerosol BDP.

Mild suppression of adrenal function can occur if more than 1600 μg/d of BDP is used.[29] The drug is reported to be safe during pregnancy when recommended doses are used.[40] When flunisolide nasal

solution and BDP were used together, two independent groups reported that there were no significant additive effects on plasma cortisol levels or on frequency of oral candidiasis.[41,42] Although a decrease of serum IgG may occur with the use of BDP, there is no reported increase in the occurrence of bacterial infections.[43]

Triamcinolone Acetonide

Triamcinolone acetonide (Azmacort, Rorer) is a nonpolar, water-insoluble fluorinated steroid that has recently become available for commercial use in the United States. It comes in an aerosolized form in an MDI attached to a barrel-shaped spacer. As previously discussed, initial trials with water-soluble corticosteroids, such as dexamethasone phosphate, did not show any significant advantage over oral steroids,[3,11,13] however, development of nonpolar, water-insoluble preparations of topical steroids would be expected to have distinct advantages over water-soluble ones in that they have less potential for systemic absorption and thus have a lower risk of side effects.[34,45] Topical antiinflammatory potency of triamcinolone acetonide (Figure 2) is less than that of BDP.[36,37]

The manufacturer of triamcinolone acetonide aerosol (TAA) designed a special spacer delivery system that minimizes deposition of drug in the oral cavity and increases efficiency of drug access to the lungs. One puff of this aerosol releases 200 μg of TAA, 100 μg of which are delivered from the unit to the airways as a fine suspension. The recommended daily dose is 2 inhalations 3–4 times a day. In delivered doses ranging from 400–2000 μg d, TAA has proved to be effective therapy for asthma in both long-term and short-term studies.[46–53]

The efficacy and safety of TAA in steroid-dependent asthmatic patients were studied by Bernstein et al in a multicenter, short-term controlled and long-term open study.[52] Patients treated with TAA in doses of 800–1600 μg d showed highly significant improvement from baseline in pulmonary function tests and in asthmatic symptoms, whereas no significant improvement was observed in patients treated with placebo aerosol. Mean changes in plasma cortisol level were not statistically significant after 1 year. The only significant side effects reported in this study were hoarseness and sore throat.

Three long-term studies (3–26 months) investigated the effects of TAA in reducing oral steroid requirements in heavily steroid-dependent patients.[47–49] Forty percent to 70% of patients discontinued the use of oral steroids and were maintained solely on TAA. Several patients developed symptoms of adrenal insufficiency while tapering prednisone, but some demonstrated disappearance of cushingoid features as well as improvement in asthmatic symptoms.[49] Minimal side effects of mild hoarseness and periodic loss of voice in 1 patient were observed.[49]

In four short-term studies of 4–12 weeks' duration, TAA was studied for its effectiveness in controlling asthma symptoms and the feasibility of eliminating or reducing oral steroids.[46,50,51,53] In doses ranging from 400–1400 μg d of TAA, asthma remained under satisfactory control, pulmonary function improved significantly, oral steroids were either reduced or totally withdrawn and plasma cortisol levels increased in three out of four studies. Oral candidiasis was reported in 2 patients in one of these studies.[50] Treatment of asthma in children with TAA was also reported to be successful, with no evidence of adrenal suppression.[54] Side effects are minimal, since there is a low frequency (2.5%) of hoarseness and oral candidiasis.[55]

Flunisolide

Flunisolide is another synthetic corticosteroid with potent antiinflammatory activity. The aerosolized form has been studied for the treatment of asthma. Its systemic potency is equivalent to that of triamcinolone and is about 5 times greater than that of cortisol.[56] It is fluorinated in the 6 position and is polar because of cyclized acetonide in the 16 and 17 positions (Figure 2). Flunisolide aerosol was recently approved by the Food and Drug Administration and will be marketed under the trade name of Aerobid by Key Pharmaceuticals.

Pharmacokinetics

Pharmacokinetic properties of flunisolide have been determined in healthy volunteers. The drug is absorbed through pulmonary membranes, and buccal and intestinal mucosae.[57] Systemic availability of a single inhaled dose (1 mg) of flunisolide was 30–40%. Peak plasma concentration was achieved in 2 minutes and maintained at approximately this level for about an hour. The elimination rate of flunisolide was similar after administration by intravenous, oral and inhalation routes with the terminal elimination half-life being 1.82 ± 0.42 hours. Rapid degradation of systemic flunisolide occurred by extensive first-pass metabolism to the 6 β-OH metabolite and other water-soluble conjugates, which are relatively inactive.[58]

The rapid metabolism of flunisolide apparently accounts for its low systemic toxicity. The drug can be administered in therapeutically effective doses for several months in adults and children without their showing significant systemic effect (see section below).

The relative potencies of intravenous:oral and intravenous:inhalation routes for flunisolide are 6:1 and 3:1 respectively, as assessed by its suppression of eosinopniis.[57]

Clinical Efficacy

Clinical investigators have reported effective results of flunisolide aerosol for asthma in both blinded and open studies of adults and children.[59–64] In three separate double-blind trials conducted in adults with chronic asthma, flunisolide aerosol ranging from

0.8–2 mg daily applied in 2 separate doses was compared with placebo for 3 weeks to over 1 year. The investigators found statistically significant differences in favor of flunisolide in major therapeutic responses: improvement in spirometric function and daily symptom scores, reduction or elimination of oral steroids and reduction of nonsteroidal asthma medications.[62–64] Some patients developed oral candidiasis when flunisolide was used for over a year, but there were no major adverse clinical reactions or laboratory abnormalities.

In another double-blind multicenter study in adults with steroid-dependent asthma, 40 patients received 1 mg/d flunisolide aerosol and 33 received placebo for 16 weeks.[65] There was a significant difference in the decreases in median oral prednisone dosage between the study groups: 74.4% in the flunisolide group compared to only 4.2% in the placebo group. Complete withdrawal of oral steroids was achieved in 27.5% of flunisolide-treated patients and in 12.1% of patients receiving placebo. Reduction in the frequency of asthmatic attacks also favored those treated with flunisolide. Although there were no statistically significant differences in asthma severity between the groups prior to the study, a decrease in severity occurred during the study in both groups, but was greater in the patients receiving flunisolide.[65] These patients were also associated with an increase in plasma cortisol level (43%), but no change was observed in the placebo group. The authors concluded that flunisolide aerosol (1 mg/d) provided superior symptomatic control and replaced an average of 9 mg/d of oral prednisone without causing serious adverse local or systemic effects.

Webb et al obtained similar results.[56] In a 3-month study, they studied the efficacy of flunisolide aerosol in 16 steroid-dependent and 13 steroid-independent patients with asthma. Each patient received 2 mg of flunisolide daily by aerosol (four 250-μg puffs twice daily). Adrenal function was monitored with repeated measurements of plasma cortisol levels and metyrapone tests. The steroid-dependent patients demonstrated a significant decrease in use of prednisone (61%) and adrenergic aerosol, improved pulmonary function and a significant increase in morning plasma cortisol levels (33%). Steroid-independent patients had significant improvement in forced expiratory volume in 1 second (FEV$_1$) and a decrease in the use of theophylline and adrenergic aerosols. They had no change in morning cortisol levels, however. Side effects, which were minimal in both groups, included throat irritation, abdominal bloating and the appearance of nasal polyps and rhinitis in some steroid-dependent patients after discontinuing systemic steroid therapy.[56]

Efficacy of flunisolide aerosol was also addressed in pediatric populations.[61, 66, 67] Shapiro and associates studied 32 steroid-dependent asthmatic children for a period of 12 weeks using a double-blind, prerandomized method.[61, 67] The drug-treated group received 0.5 mg of flunisolide aerosol twice a day. All patients receiving flunisolide had improved asthma control and a significant decrease in oral steroid dosage. Only half of the placebo-treated control group had a decline in steroid requirements. Pulmonary function tests and adrenal function remained stable in both groups. Patients in both groups developed some pharyngeal candidiasis, but this could have been related to previous steroid use in some of them.

Meltzer and others conducted another short-term, double-blind, placebo-controlled study lasting 8 weeks. The 46 steroid-independent asthmatic children[66] received either 0.5 mg flunisolide aerosol or placebo twice a day. Effectiveness was evaluated by daily symptom scores, pulmonary function and physical examination. Most symptom scores (severity of wheezing, chest tightness, shortness of breath and frequency and severity of asthma attacks) were significantly better in those receiving flunisolide than in those receiving placebo. Pulmonary function showed improvement in the flunisolide-treated group and deterioration in the placebo group, but these differences were not statistically significant. No serious adverse effects were reported. No patient developed thrush or evidence of adrenal suppression.

Gale and co-workers evaluated the effects of concurrent administration of flunisolide and beclomethasone in patients with both rhinitis and asthma.[44] Flunisolide *nasal* solution was added to either BDP bronchial aerosol or flunisolide bronchial aerosol to study the possible cumulative effects of topical corticosteroids on adrenal function. The investigators also evaluated the efficacy of these combinations in controlling symptoms associated with rhinitis and asthma for 1 month. Patient and physician assessments revealed no significant differences between the combinations in efficacy, adverse effects or effect on adrenal function.

The frequency of oropharyngeal candidiasis in patients using flunisolide aerosol and BDP was studied by Spector and colleagues.[68] Symptomatic thrush was slightly more common ($p = 0.03$) in patients treated with BDP (200 μg 4 times a day) compared to those taking flunisolide (500 μg twice a day). Patients with pretrial throat cultures that were positive for candida organisms had significantly greater frequency of clinical thrush than those with negative cultures. Positive pretrial throat cultures provided a good indication of patients at higher risk of developing thrush; they might benefit from more frequent and prolonged mouthwashes after using corticosteroid aerosols.

Budesonide

Budesonide is an investigational 16α, 17α-acetal corticosteroid that is not halogenated (Figure 2). It has a high degree of topical antiinflammatory activity and low systemic potency.[69] After topical application, it was 2 times as potent as beclomethasone and 3 times as potent as flunisolide in inducing vasoconstriction.[69] It lacks the halogen substitution that is present in flunisolide, triamcinolone and beclometh-

asone. Since this substitution decreases the rate of biotransformation, budesonide is rapidly metabolized[65] (Table 2).

Pharmacokinetics

Within seconds after the drug was administered by bronchial inhalation in healthy volunteers, unchanged budesonide was detected in blood plasma, indicating that the drug is absorbed intact through the respiratory tract.[70] This initially high plasma concentration also indicated minimal metabolism of drug in the lung. Plasma half-life of unchanged budesonide was estimated to be 2.0 ± 0.2 hours, a value similar to that found after intravenous injection (2.8 ± 1.1 hr).

Human pharmacokinetic studies showed that budesonide is readily biotransformed in the liver by oxidative and reductive biotransformation, but not in the lung or skin.[69] The systemic availability after oral administration was calculated to be 10.7 ± 4.3%. Extensive first-pass metabolism occurred as the drug biotransformed rapidly when incubated with human liver.[71] In vitro biotransformation studies in human liver isolated two major metabolites, 6 β-hydroxybudesonide and 16 α-hydroxyprednisolone.[71] They are virtually inactive and were 1/10 to 1/100 weaker than the parent compound. Plasma protein binding was around 88%. Recovery studies in humans after inhalation of ^{3}H budesonide showed that most of the radioactivity was excreted in the urine (32%) and feces (15%).[72] About 40% of the administered dose was deposited in the inhaler and about 5% was deposited in the oral cavity.

Pharmacologic studies in rats showed that the ratio of topical to systemic effects of budesonide was 10–20 times better than that of BDP and TAA[73] (Table 1). Such improvement makes budesonide a promising alternative for aerosol treatment of asthma.

Eliul-Micallef et al administered 1 mg of budesonide by inhalation to 12 patients with chronic bronchial asthma and studied responses over time.[74] Two hours after drug inhalation, a statistically significant increase in peak expiratory flow (PEF) occurred. Peak effect occurred between 6 and 7 hours after budesonide inhalation and the change in bronchial function was still significant for up to 12 hours.

Comparative Studies

The clinical efficacy of aerosol budesonide in bronchial asthma has been compared satisfactorily with that of aerosol BDP, subcutaneous terbutaline and oral prednisolone.[71–75]

In open short-term, crossover trials, budesonide was compared to BDP in 27 steroid-dependent asthmatics.[72] Both drugs were given in the same dosage of 200 μg 4 times a day for 2 weeks and no significant differences were noted between them. The report did not mention any side effects.

Willey et al performed a well-designed, double-blind crossover trial comparing 100 μg of BDP 4 times a day and 200 μg of budesonide 2 times a day in 30 chronic asthmatics.[74] Each treatment regimen was studied for 4 weeks. Assessments consisted of daily scores of asthma severity and morning and evening PEF values. Every 2 weeks the authors measured forced vital capacity (FVC) and FEV_1. There were no significant differences in PEF values during the study period. Although FEV_1 values were slightly higher after budesonide therapy ($p < 0.05$), FVC values showed no significant differences. During the 8 weeks, there were no clinically significant systemic side effects or cases of oropharyngeal candidiasis. Similarly, symptom scores between the groups showed no significant differences. Thus budesonide 200 μg twice a day was at least as effective as BDP 100 μg 4 times a day in controlling asthma symptoms.

Table 2. Plasma Half-lives of Various Corticosteroids

Corticosteroid	Plasma Half-life (min)
Cortisone	90
Cortisol	90
Flunisolide	100
Budesonide	150
Prednisolone	200
Methylprednisolone	200
Triamcinolone	200
Dexamethasone	300
Betamethasone	300
Beclomethasone dipropionate	900[a]

Adapted from references 60 and 81.
[a]From reference 81.

Dahl and Jonansson performed double-blind, placebo-controlled study in 21 asthmatics to investigate the clinical effects of inhaled budesonide and subcutaneous terbutaline given separately or simultaneously.[75] Terbutaline produced a faster onset of bronchodilation than budesonide (1 hr vs 4 hrs) as indicated by changes of PEF. The peak increase in PEF after either drug favored terbutaline. The two drugs given simultaneously did not show potentiation or additive effect.

Contrary to the above study, Henriksen and Dahl found that when inhaled terbutaline 32.5 μg and inhaled budesonide 400 μg d were given together to 14 children with exercise-induced asthma, the drug combination exerted an additive effect on improving pulmonary function.[76] The authors also concluded that 1–4 weeks of treatment with inhaled budesonide decreased the severity of asthma in these children. No side effects were reported.

Several short-term trials studied the clinical effects after oral prednisolone and inhaled budesonide in asthma patients.[71–75] The investigators found that 400 μg of budesonide had the same effect on PEF as did 10 mg of prednisolone, whereas 800 μg of bude-

sonide was as potent as 20 mg of prednisolone.[75] However, the authors did not specify the statistical methods used to evaluate the data. Another double-blind trial administered 40 mg prednisolone orally, placebo orally and 1 mg of budesonide by inhalation. Oral prednisolone produced a statistically significantly greater effect on PEF from the eighth hour after drug administration onward.[71] The peak effect occurred between 6 and 7 hours after budesonide inhalation and about 9 hours after prednisolone. Oral prednisolone 40 mg also produced a significantly greater maximal response in PEF, but the response peaked 3 hours later than budesonide.

Budesonide exerted a dose-dependent suppression of blood eosinophils and plasma cortisol levels.[38, 77] This change is significant if budesonide is used in doses of 1600 μg·d.[77] The drug has less systemic effects on eosinophils and plasma cortisol levels when compared with BDP.[69, 77]

Dosing Frequency

Several investigators studied the influence of dosing frequency on the efficacy of aerosol budesonide in asthmatic patients. The results were contradictory.[73, 77, 78] Data from Toogood et al showed that the same daily dose given in different dosing schedules did not affect the drug's systemic potency but it did affect its antiasthmatic potency.[77] Twice-daily dosing was associated with reduction in drug potency as indicated by the drop in daily PEF and increase in severity of symptoms.[77] This agreed with the findings of Dahl and Jonansson[78] but contrasted with those of Stiska et al.[72] who claimed that reduction of the frequency of inhaled budesonide did not reduce the effect of the treatment. As asthma became more severe, however, dosing frequency became a major response-limiting factor, and could not be offset despite a fourfold increase in daily dosage.[77, 79] Less frequent dosing decreased the prevalence of oropharyngeal candidiasis.[77] Overall, administration 4 times a day provided the best risk-benefit relationship.

Current Rationale and Recommendations for Corticosteroid Aerosols

Many controlled studies have shown that corticosteroid aerosols such as beclomethasone dipropionate, triamcinolone acetonide, flunisolide and budesonide are highly effective in the control of asthma. All of these agents have high topical activity, low systemic activity and rapid hepatic metabolism (Table 1 and 2). Side effects are minimal, the major ones being oral thrush and hoarseness. Used within the normal range, these drugs rarely suppress adrenal function and are safe for both adults and children.

Theophylline derivatives, beta-agonistic bronchodilators and cromolyn sodium should all be tried before either aerosol or systemic steroids are administered.[82, 83] Some patients may require the use of bronchodilator aerosol 10–15 minutes before inhaling a steroid aerosol, thus allowing the aerosol to penetrate deeper into the peripheral airways. Short courses of systemic steroids may be necessary during periods of stress or reduced airway patency. Immunotherapy should not be stopped during treatment with oral or inhaled steroids.

Patients should be reminded that aerosol steroids are for prophylactic use only and should be used regularly to prevent asthma. These preparations should not be used during an acute attack of asthma because a smaller fraction of the dose will be inhaled due to airway obstruction.

Finally, all patients taking steroid aerosols should be observed and instructed by both physicians and pharmacists about the proper use of the inhaler spacer in order to experience optimal therapy.

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